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Memory T Cells

Nelson Chao

Division of Cellular Therapy, Duke University Medical Center, Durham, North Carolina

Corrrespondence and reprint requests: Nelson Chao, MD, Division of Cellular Therapy, Duke University Medical Center, BMT, Box 3961, Durham, NC 27710 (e-mail: chao0002@mc.duke.edu).

Memory… is the diary that we all carry about with us.
~Oscar Wilde, "The Importance of Being Earnest"

And so it is with the immune system. Memory T cells are a critical component of the adaptive immune system. Our ability to respond rapidly to antigens/pathogens that we have been exposed to previously is at the heart of the adaptive immune system. In general, these memory T cells allow protection of the host to pathogens that the individual has previously encountered and/or been vaccinated against. The secondary response is rapid and more potent, leading to a rapid clearance of the offending agent. Not surprisingly, this population has also been explored in their contribution to graft-versus-host disease (GVHD).

T CELLS IN HEMATOPOIETIC CELL TRANSPLANTATION

T cells have been clearly implicated in the pathogenesis of acute GVHD (aGVHD). There are extensive clinical data demonstrating that rigorous T cell depletion (TCD) abrogates aGVHD. Unfortunately, in many clinical settings, this process can result in loss of facilitation of engraftment as well as high incidence of relapses because of the loss of the graft-versus-tumor effect.

The ability of the host to recover normal adaptive immunity is a centerpiece for successful allogeneic hematopoietic stem cell transplantation (HSCT). The recovery of normal T cells is a portion, albeit an important one, of normal immunity. The other cells are also important such as dendritic cells, B cells, monocytes, macrophages, and the recovery of the innate immune system. Recovery of normal numbers of T cells and normal function is governed by many factors such as the type of preparatory regimen, the status of the thymus and secondary lymphoid organs, homeostatic proliferation of donor and residual recipient T cells, regulation of T cell apoptosis, presence of harmful immunesuppressants such as calcineurin inhibitors or steroids, or possible beneficial immunesuppressants such as sirolimus.

T CELL DEVELOPMENT

The ontogeny of T cells and its T has been extensively studied [1-4]. T cells are generated from hematopoietic stem cells (HSC) found in the bone marrow. Common lymphoid progenitors give rise to T cell precursors or immature thymocytes. These cells populate the thymus initially as double negative cells ($CD4^-CD8^-$). As these cells mature, they become double positive ($CD4^+CD8^+$) before becoming mature T cells that are single positive ($CD4^+$ or $CD8^+$). These single positive cells then egress from the thymus into the peripheral circulation.

The majority of the immature thymocytes actually never leave the thymus. There is an intricate tightly regulated 2-step selection process that determines which T cells will be found in the circulation [5]. The first step is termed positive selection. Here in the cortex of the thymus, the double positive T cells that can bind self-antigens in the context of the appropriate major histocompatibility complex (MHC) of the host's thymic epithelial cells are given a survival signal. Those cells that bind MHC class II molecules become single positive $CD4^+$ cells, whereas those that bind MHC class I will become single positive $CD8^+$ cells. All the other T cells that are not able to bind self-antigens undergo apoptotic cell death.

This first step is fraught with the danger of engendering autoimmune T cells because each of the positively selected T cell can recognize self-antigens. Thus, a second equally negative selection step needs to occur. In this process, the positively selected thymocytes move to the medulla where they are presented with self-antigens in the context of the appropriate MHC by professional antigen-presenting cells (APCs) such as dendritic cells or macrophages. Those cells that bind with too high affinity to self-antigens are given a signal to undergo apoptosis. This process ensures that the majority of the highly autoreactive T cells do not slip into the peripheral blood where they may wreck havoc by causing an autoimmune process.

During this process, a small number of T cells become regulatory T cells as well.

NAÏVE VERSUS MEMORY T CELLS

T cells that have undergone positive and negative selection egress from the thymus into the circulation. These cells will circulate sampling antigens presented in the context of their respective MHC molecules. Naïve cells are fully mature T cells, but have not yet encountered the appropriate antigen that its T cell receptor can recognize. Naïve T cells express L-selectin (CD62L) and lack or have low expression of CD44 and activation markers such as CD25 and CD69. They also do not have any of the edited isoforms of CD45 (they are CD45RA versus memory T cells are CD45RO or RB). Naïve cells are thought to be relatively quiescent and do not divide until they encounter their antigen. They require IL-7 and IL-15 for homeostatic survival.

Naïve T cells remain in this quiescent stage until they encounter the specific antigen to which its T cell receptor is targeted. The recognition of its cognate antigen triggers the naïve T cell to respond. If secondary signals in the form of costimulatory molecules occurs, that cell initiates the adaptive immune response. The naïve T cells produce IL-2, proliferate, and acquire an activated phenotype ($CD25^+$, $CD44^+$, $CD69^+$) with a drop in the expression of L-selectin ($CD62L^{low}$). This response may occur in a $CD4^+$ cell leading to a helper T cell response or in a $CD8^+$ cell leading to a cytotoxic response.

Encounter with the specific antigen drives a significant proliferation of the specific T cell clones to respond against the antigen. For example, if a patient develops influenza for the first time, then the specific naïve T cells for the immunodominant influenza peptides will proliferate. The $CD4^+$ helper T cells produce cytokines and the cytotoxic $CD8^+$ cells will destroy cells infected with the influenza virus and rid the host of the infection. In this process, many of these antigen specific cells will undergo apoptosis. As the infection dies down (ie, there is a drop off in the amount of influenza specific antigen), some of the antigen specific cells will become memory T cells, whereas others will become regulatory T cells, thus decreasing the nflammatory immune response.

Memory T cells are those lymphocytes that have encountered antigen and mounted a response against such an antigen and thus are no longer antigen naïve [6]. These cells are also normally in a quiescent state. If they encounter the same specific antigen, for example the same influenza virus, they will produce a rapid and robust immune response characterized by prompt proliferation, production of inflammatory cytokines and rapid clearance of the virus.

There are at least 3 populations of $CD8^+$ memory T cells and probably similar $CD4^+$ cells. Broadly speaking, they are central versus effector memory T cells [7]. Central memory T cells are thought of as memory "stem cells." These cells tend to be long lived and carry the essential imprint of previous antigen exposure. These cells are thought to give rise to long-lived immunologic memory. The cells express L-selectin ($CD62L^+$) and the chemokine receptor CCR7. They secrete IL-2 but not IL-4 or interferon-gamma.

Effector memory T cells tend to express molecules with cytotoxic function. These effector memory cells (T_{EM} or T_{EMRA}) tend to produce cytokines such as interferon-gamma and IL-4. The T_{EM} cells do not express CD62L or CCR7. Although CD45RA isoforms have been used to differentiate naïve (CD45RA) from memory T cells (CD45RO), some of the memory T cells will revert back to CD45RA and thus this marker alone is not absolute.

MEMORY T CELLS AND PREVENTION OF GVHD

As mentioned above, T cell depletion (TCD), whereas effective, can be associated with higher incidence of infection, lack of engraftment and relapse. There have been many attempts to parse the T cell subsets in different manners to overcome some of the concerns regarding these 3 complications. Examples of these include use of CD4, CD8, CD6, CD25, and CD69 positive or negative selection process for the initial graft as well as use of such markers for donor lymphocyte infusions. Some of these approaches remain promising in early trials. One other method could be to parse T cells into a memory versus a naïve phenotype to ascertain whether there is a difference in the incidence of GVHD based on these 2 broad T cell populations. What follows later from the summaries of Drs. Shlomchik and Chen are our current understanding of the contributions of the population of naïve versus memory T cells in aGVHD models and in human mixed lymphocyte cultures. It is hoped that such approaches will allow the beginnings of engineering a graft that contains most of the positive cellular components without the allospecific GVHD inducing cells.

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Memory T Cells in GVHD and GVL

Britt E. Anderson,[1] Hong Zheng,[2] Patricia A. Taylor,[3] Catherine Matte-Martone,[4] Jennifer M. McNiff,[5] Dhanpat Jain,[6] Anthony J. Demetris,[7] Angela Panoskaltsis-Mortari,[3] Ann Ager,[8] Bruce R. Blazar,[3] Mark J. Shlomchik,[9] Warren D. Shlomchik[10]

[1]Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut; [2]Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania; [3]Cancer Center and Department of Pediatrics, Division of Bone Marrow Transplantation, University of Minnesota, Minneapolis, Minnesota; [4]Section of Medical Oncology, Cancer Center, Yale University School of Medicine, New Haven, Connecticut; [5]Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut; [6]Department of Pathology, Yale University School of Medicine, New Haven, Connecticut; [7]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [8]Department of Medical Biochemistry and Immunology, School of Medicine, Cardiff University, Cardiff, UK; [9]Departments of Laboratory Medicine and Immunobiology, Yale University School of Medicine, New Haven, Connecticut; [10]Section of Medical Oncology, Cancer Center and Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut

We and others have recently shown that T_{EM} do not cause graft-versus-host disease (GVHD) in MHC-matched and MHC-mismatched mouse strain pairings [1-4]. Yet, after transfer, memory T cells can mount an appropriate recall response in the recipient. However, there is no a priori reason to suppose that the essential features of memory phenotype cells will be different, even if a larger component of mouse cells with this phenotype arose by homeostatic proliferation [5,6].

We have been avidly investigating why $CD44^+CD62$ ligand $(CD62L)^-T_{EM}$ do not mediate GVHD. At least 3 nonexclusive hypotheses could explain this finding. First, T_{EM} may not traffic sufficiently to lymph nodes (LN) and Peyer's patches (PP) because of reduced expression of CD62L (also known as L-selectin) and/or CC-chemokine receptor 7 (CCR7). Implicit in this idea is that these are required sites for priming of T_N. Second, T_{EM} may have a more restricted TCR repertoire that reduces the frequency of alloreactive T cells below the threshold necessary to induce GVHD. That T_{EM} fail to induce GVHD in MHC-mismatched models, in which the overall frequency of alloreactive T cells among T_N is as high as 10%, makes this unlikely to be the only explanation, although this hypothesis has not been fully excluded. Also, as T_{EM} can mediate graft-versus-leukemia (GVL) (see below) and respond in mixed lymphocyte reactions against allogeneic stimulators indicates that alloreactive cells are present among T_{EM}. Third, intrinsic properties of T_{EM}— for example, reduced clonal expansion—could prevent the development of the complete GVHD syndrome [4].

We have addressed the trafficking hypothesis in some detail. To do so we used T cells deficient in CD62L or CCR7, transplant recipients lacking PNAd ligands for CD62L, and recipients without LN, PP, or LN, PP, and spleen. Surprisingly, functional CD62L and CCR7 were not required for T_N-mediated GVHD. Indeed, $CCR7^{-/-}$ T cells induced GVHD in recipients lacking PNAd ligands. We hypothesized that $CD62L^{-/-}$ T cells might have been primed in the spleen; however, $CD62L^{-/-}$ T cells induced GVHD in splenectomized recipients. In multiple strain pairings GVHD developed in recipients that lacked LN and PP. Mild GVHD could even be induced in mice lacking all major secondary lymphoid tissues (SLT). We unexpectedly observed in several cases that altering the trafficking and priming site of donor T cells affected the nature of GVHD. This phenomenon manifested both when priming occurred in the absence of the spleen or the PP/LN. In 3 MHC-mismatched models, LN/PP-intact but splenectomized recipients developed more rapidly lethal GVHD than WT (spleen intact) recipients. In the 129 → B6 MHC-matched model, the lack of LN/PP promoted the development of cutaneous GVHD. Conversely, enforced constitutive expression of CD62L on T_{EM} did not endow them with the ability to cause GVHD. Taken together, these data argue against the hypothesis that T_{EM} fail to induce GVHD because of inefficient trafficking to LN and PP. Moreover, these data indicate that no specific site of priming is essential for GVHD induction, although the GVHD phenotype can be altered in the absence of individual SLTs.

We have also investigated whether $CD4^+$ T_{EM}, unprimed to recipient antigens, mediate GVL. We performed these experiments in an the MHCII-mismatched $B6^{bm12}$×B6 strain pairing to parallel the dominant form of allorecognition in haploidentical alloSCT. $CD4^+$ T_{EM} mediated GVL against mouse models of chronic phase and blast crisis chronic myelogenous leukemia (without causing GVHD), although they were less potent inducers of GVL than were T_N. By creating gene-deficient leukemias and using perforin-deficient T cells we found that direct cytolytic function is essential for T_{EM}-mediated GVL, but that GVL is retained when killing via FasL, TNF-α, TRAIL, and perforin are individually impaired. However, T_{EM}-mediated GVL was diminished when both FasL and perforin pathways were blocked. In sum, these results suggest that T_{EM} retain sufficient cytolytic function to mediate GVL but lack other properties (eg., sufficient clonal expansion) required to establish GVHD.

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Allogeneic Memory T Cell Response

Benny J. Chen

Division of Cellular Therapy/BMT, Duke University Medical Center, Durham, North Carolina

One of the central features of the immune system is the ability to maintain memory after exposure to antigen [1-3]. However, results from several independent studies published in the past several years suggest that memory T cells do not cause graft-versus-host disease (GVHD) [4-8]. These results have also led investigators to study further the ability of allospecific memory T cells to induce GVHD [9-12]. In this review, we describe the ability of nonalloreactive, crossreactive, and allospecific memory T cells to induce GVHD and how these new concepts can be applied in allogeneic hematopoietic cell transplantation.

NONALLOREACTIVE MEMORY T CELLS

The specificity of a memory T cell is determined by the T cell receptor that is produced by random gene rearrangement in thymus before it encounters the specific antigen [13]. Because naïve and memory T cells are exclusive T cell subsets, memory T cell subset should not contain host-antigen-specific T cells and should not be able to induce GVHD if the donor has not encountered antigens present in the host. Our group has further demonstrated that, similar to effector memory T cells, central memory T cells are unable to induce GVHD. GVHD-inducing T cells are exclusively contained in naïve phenotype T cells [8]. Because most of the memory T cells if not all are nonalloreactive in unprimed donors, the data described above confirm that nonalloreactive T cells do not induce GVHD.

CROSSREACTIVE MEMORY T CELLS

Even though it is very clear from the animal studies that memory T cells from unprimed donors do not contain allospecific T cells and do not cause GVHD [4-8], concerns about the risk of GVHD remains especially when this approach is translated into humans because the existence of nonallospecific but crossreactive T cells [3]. These crossreactive T cells could be activated by different environmental antigens and likely crossreact with a wide variety of different epitopes or different antigens. Thus, the alloresponses induced by these cells will likely vary dramatically between different donor-recipient pairs. Because of this, it would be difficult to predict how different crossreactive memory T cells react to alloantigens in GVH reaction. However, there is evidence to suggest that crossreactive memory T cells also have dramatically decreased ability to induce GVHD [8]. Crossreactive memory T cells do exist in unprimed donors because equal IL-2 production was detected in purified memory T cells upon challenge with alloantigens despite

the low proliferation and cytotoxicity as measured by the optimal 5-day cultures, but these memory T cells that are crossreactive to host antigens are unable to cause GVHD. Although the reason why these crossreactive T cells cannot induce GVHD has not been completely elucidated, it is known that the alloresponse mediated by these memory T cells cannot be maintained in 5-day mixed lymphocyte cultures.

ALLOSPECIFIC MEMORY T CELLS

Another concern of selection of memory T cells is the existence of true allospecific memory T cells in some donors. Allospecific memory T cells can be generated after exposure to alloantigens in the form of blood transfusion, prior transplantation, or pregnancy [14]. Following organ transplantation, allospecific memory T cells mediate faster and stronger immune response than naïve T cells [15]. In GVHD, results from 2 different groups suggest that allospecific memory T cells have decreased ability to induce GVHD compared with naïve T cells [9,10]. To generate allospecific memory T cells, we first primed the donor C57BL/6 mice with irradiated host BALB/c splenocytes. More than 8 weeks later, we harvested T cells from spleen and sorted them into naïve and memory T cells subsets based on their expression of CD62L. The results demonstrate that $CD62L^-$ from primed donors, which mediate stronger in vitro proliferative response, have decreased ability to mediate GVHD compared with $CD62L^+$ cells harvested from the same animals. In contrast to unprimed donors, $CD62L^-$ T cells from primed donor are able to induce GVHD. Similar results have also been presented by Dutt et al. [10]. It is important to point out that these data are contrary to the data published by Zhang et al. [11,12]. This group has demonstrated that allospecific memory T cells harvested from GVHD mice have increased ability to induce GVHD compared with naïve T cells. It is currently unclear why allospecific memory T cells harvested from immunized donors and from GVHD mice have different ability to induce GVHD. Because all the current models employ a heterozygous population of memory T cells in which allospecific memory T cells represent only a small subset of total T cells, a cleaner system such as those using allospecific T cell repertoire (TCR) transgenic T cells may be needed to answer this question more definitely.

EFFECT OF MEMORY T CELLS ON ENGRAFTMENT, IMMUNE RECONSTITUTION, AND ANTITUMOR RESPONSE

Results from pan T cell depletion (TCD) studies indicate that the goal of any approach for prophylaxis and treatment of GVHD is not only to prevent GVHD, but also to preserve the beneficial effects mediated by T cells such as the antimalignancy as well as antimicrobial effects [16]. Understanding the effects of memory T cells on immune reconstitution, stem cell engraftment, and antitumor effects would be important prior to development of clinical trials.

Immune Reconstitution

T cell reconstitution posthematopoietic cell transplantation primarily occurs through peripheral expansion of mature T cells contained in the graft and/or thymopoiesis [17]. We and others have demonstrated that effector memory T cells can contribute directly to posttransplantation T cell recovery [4,5]. We have further demonstrated that memory T cells from unprimed donors promote the generation of new T cells from stem/progenitor cells [4]. These observations have indicated that memory T cells contribute to posttransplantation T cell reconstitution not only through peripheral expansion but also through thymopoiesis. These important observations suggest that memory T cells are capable of protecting the stem cell recipients from infections early after transplantation by providing immediate recall immunity and later by enhancing more diverse T cell regeneration through thymopoiesis. Allospecific memory T cells are expected to provide some early protection but would likely impair thymopoiesis because they can induce GVHD.

Engraftment

We also observed that host radioresistant T cells were depleted in memory T cell recipients but not in the T cell-depleted bone marrow control mice [4], suggesting that memory T cells may be able to facilitate donor stem cell engraftment by reducing host immune resistance. The observation that memory T cells are able to respond initially but fail to maintain the response (see above for detail) may explain why memory T cells are able to deplete host radioresistant cells without causing GVHD. Most likely, this unique feature of memory T cells is caused by crossreactive memory T cells in response to alloantigens. Further studies are required to understand this unique response.

Antitumor Effect

Initial results from proliferation assay suggest that, similar to the response against alloantigens, unprimed memory T cells' response to tumor antigens is also minimal [4]. Subsequent in vivo experiments have demonstrated that unprimed memory T cells do have direct antitumor potential [18,19]. Even though we have not titrated the response by using quantitative in vivo titration assays, the antitumor activity mediated by unprimed memory T cells is unlikely as good as that

Table 1. *Difference in Allogeneic Memory T Cell Responses during Host-versus-Graft and Graft-versus-Host Response*

	Host-versus-Graft	Graft-versus-Host
Naïve	++	++
Nonalloreactive memory	−	−
Crossreactive memory	+++	+/−
Allospecific memory	+++	+

−indicates no response; +/−, with or without response; +, decreased response; ++, normal response; +++, enhanced response.

mediated by naïve T cells, because similar mechanisms may account for the depletion of host radioresistant cells and the inhibition of tumor growth and these same T cells do not induce GVHD. Antitumor activity by memory T cells could be enhanced by selecting a donor who naturally carry tumor-associated antigen-specific memory T cells or after vaccination of the donor in vivo or ex vivo. Because memory T cells enhance immune reconstitution through both peripheral expansion and thymopoiesis, antitumor activity could also be enhanced through vaccination post hematopoietic cell transplantation.

CLINICAL TRANSLATION

Data from animal studies have indicated that both nonalloreactive T cells and crossreactive T cells do not induce GVHD [4-8], and allospecific T cells cause less GVHD [9,10]. The major concern in using memory T cells would be nonallospecific crossreactive T cells, although in vitro testing suggest that human memory T cells ($CD45RA^{-}$) can proliferate but cannot elicit cytotoxicity against alloantigens [20]. A clinical trial will be needed to determine whether this approach can be applied in humans to prevent GVHD. The risk of GVHD might exist but should not be higher compared with infusion of bulk T cells.

SUMMARY

Recent data have revealed marked differences in alloresponses mediated by memory T cells during GVH and host-versus-graft (HVG) reactions (summarized in Table 1). Even though the mechanisms are not completely understood, it is clear that all memory T cells including nonallospecific, crossreactive, and allospecific memory T cells have decreased ability to induce GVHD. Selection of memory T cells or removal of naïve T cells will not only prevent GVHD, but could also enhance immune reconstitution, facilitate engraftment, and have the potential to enhance antitumor effects. A clinical trial has been planned. Successful translation of this approach in the clinic will improve the safety, enhance the effectiveness, and broaden the scope of allogeneic hematopoietic stem cell transplantation.

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